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CONTRACTING ORGANIZATION: University of Maryland, Baltimore
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14. ABSTRACT

The goal of this study is to identify novel imaging marker such as diffusion kurtosis that may serve as a prognostic marker in the evaluation and management of traumatic brain injury patients. This study will recruit patients patients with varying severity of traumatic brain injury (mild, moderate, severe) from the Shock Trauma center with an initial diagnosis of diffuse axonal injury. Neuropsychological testing and magnetic resonance imaging will be performed in the acute, sub-acute and chronic stages (through 6 months). The relationship between the advanced magnetic resonance imaging markers and the clinical condition of the patient will be evaluated at each time point to determine which of the imaging markers, or a combination of imaging markers are best representative of the clinical condition of the patient. Further, the markers will be evaluated for their prognostic ability to determine the clinical course of the TBI patients.

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<div align="center">**Annual Report**</div>

Grant/Cooperative Agreement Number: W81XWH-12-1-0098

Title: Evaluation of Diffusion Kurtosis Imaging in Traumatic Brain Injury

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Performance Period: Through March 2013
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Introduction
The goal of this study is to identify novel imaging marker such as diffusion kurtosis that may serve as a prognostic marker in the evaluation and management of traumatic brain injury patients. This study will recruit patients patients with varying severity of traumatic brain injury (mild, moderate, severe) from the Shock Trauma center with an initial diagnosis of diffuse axonal injury. Neuropsychological testing and magnetic resonance imaging will be performed in the acute, sub-acute and chronic stages (through 6 months). The relationship between the advanced magnetic resonance imaging markers and the clinical condition of the patient will be evaluated at each time point to determine which of the imaging markers, or a combination of imaging markers are best representative of the clinical condition of the patient. Further, the markers will be evaluated for their prognostic ability to determine the clinical course of the TBI patients.

Overall Progress

Significant delays were experienced in the establishment of the award and the approval of the IRB protocol for this project. However we are now in an active state of recruitment of patients which is progressing smoothly.
.
Protocol Modification

The IRB approvals from University of Maryland and eventually from the HRPO took significantly longer than expected. Some of the delays were related to coordination between our site and Georgetown which unfortunately has been in a flux. Since Dr. Mhyre leaving Georgetown sometime in December there have been two other personnel changes which delayed the start date for recruitment. Currently we have Dr. Fiandaca as the contact person for receiving the blood samples at Georgetown. This modification was made as recently as March 15th, 2013. We believe we have all the approvals now for us to actively recruit patients

Study Tasks

Screening and recruitment for this study has begun.
Task 1
a. Enroll patients into the study. Screening and recruitment for this study has begun. We have already recruited 16 patients into the study, but unfortunately we were not able to bank the blood samples from these patients because the bio-sample recipient site was not ready.

b. Obtain Diffusion Kurtosis images within 10 days of injury, 4 weeks and 6 months following injury. For the enrolled patients, each has completed an initial MRI (within 10 day). For some of these patients, only a standard of care MRI was able to be obtained for various clinical reasons, but for the majority we have obtained DKI images. Several of the enrolled patients have returned for their 4 week follow-up visit and undergone DKI scans. We will continue to follow enrolled patients to obtain follow-up scans.

c. Obtain data on normal control subjects. 3 healthy volunteers have been enrolled as normal control subjects, and DKI images have been obtained.

d. Obtain blood samples at the time of each MRI. Due to the above mentioned delays in coordinating with our bio-sample recipient site, we have not obtained blood samples from the enrolled patients. However, we are now in a position to begin collecting blood samples from prospectively enrolled patients.

e. Pre-process the imaging data. Convert all imaging data to standard atlas, perform regional analysis, perform histogram analysis for whole brain data, quantify DTI and kurtosis analysis quantify MRSI data, develop hemorrhagic lesion burden scale, perform image segmentation to separate white and gray matter and obtain regional volumes. Pre-processing has begun. As imaging data begin to accumulate we will begin to perform various analyses.

Processing of data will continue on an ongoing basis for both data quality monitoring purposes and to assess the general trend of the data as new data is obtained. Data is reviewed every Thursday afternoon with the team to discuss various ways to analyze data and potential for manuscript generation.

A technical presentation on the behavior of DKI when multiple diffusion weightings and multiple directions are used was presented at the International Society for Magnetic Resonance in Medicine. We investigated whether the number of directions were more important compared to the number of diffusion weightings (b-factors) in order to sample the kurtosis tensor. Our interest was also to determine the shortest acquisition time possible without losing much information regarding the tensor. It was determined that the maximum b-value of 2500 s/mm^2 and a minimum of two b-values provided a reasonable representation of the tensor for an acquisition of time of less than ten minutes. The slides from this presentation are provided in the Appendix. A manuscript of this work is near completion for submission to Magnetic Resonance in Medicine Journal.

Work During Next Reporting Period

We will now actively recruit patients for the study. We expect to recruit at the rate of about 10-15 patients a month which is about the average from the ongoing parent study. The parent study will stop recruiting any new patients and all the new patients will flow into this study. By the next quarter we hope to have about 40-50 patients recruited with about half the patients finishing their one month follow up.

Administrative Comments: We hope that all the administrative issues are behind us and can actively recruit patients. At this time there are no administrative comments.

APPENDIX

Optimal Diffusion Kurtosis Imaging for Clinical Use – Fewer diffusion weightings or diffusion directions?

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MARYLAND

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Introduction

- Diffusion Kurtosis Imaging (DKI)[*] measures the non-Gaussian behavior of water diffusion and has gained much interest lately as a tool to reveal significantly more tissue microstructure information, over and above which can be achieved from than Diffusion Tensor Imaging (DTI)

- However clinical application of DKI faces a major challenge, as it involves long acquisition times (~20 min) due to more complex model (21 model parameters vs. 6 in DTI)

- Little is known about how different DKI imaging schemes affect the variability in estimated DKI parameters
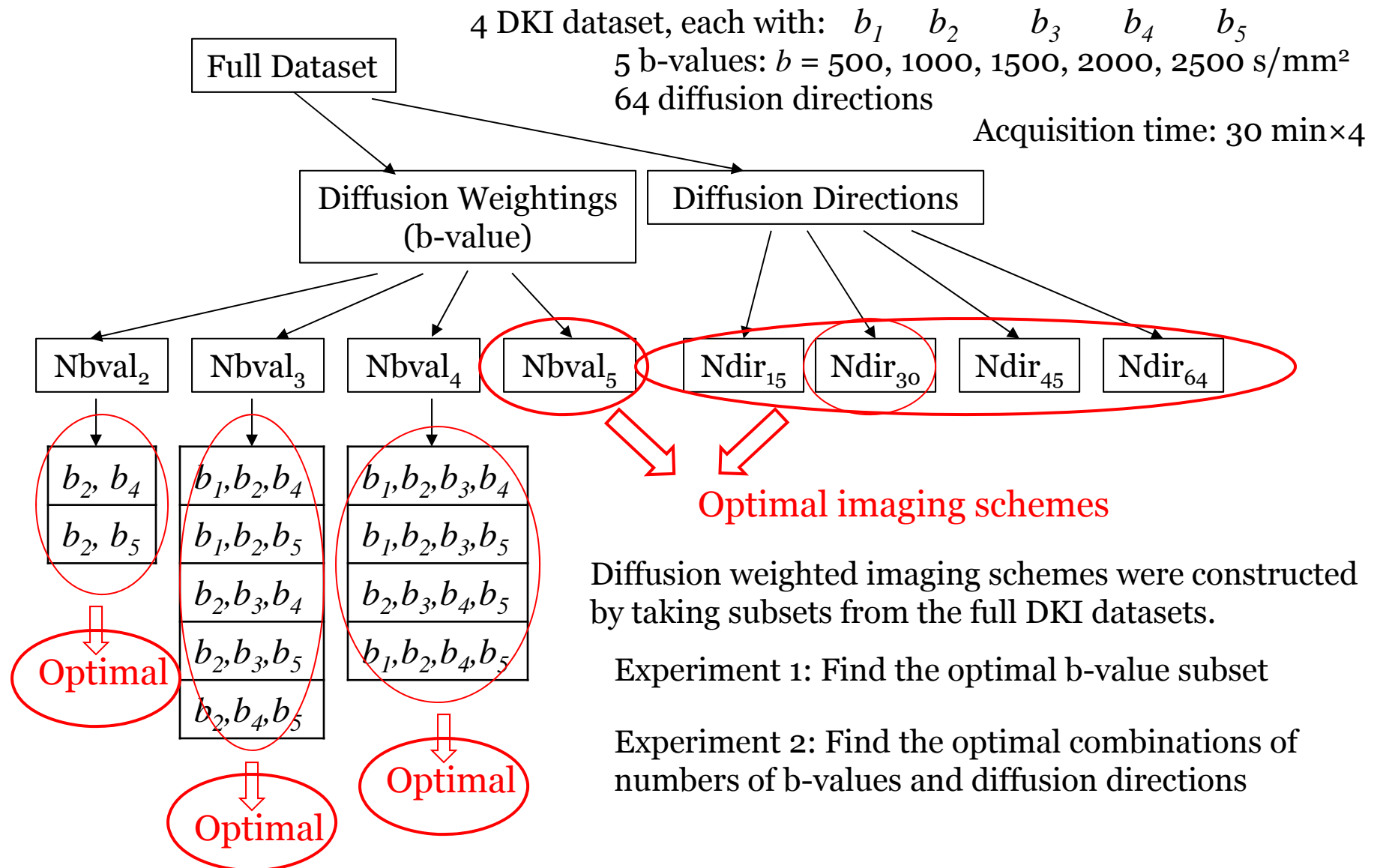
* Jensen JH, et al. 2005

Goal of this study

- To study the effect of imaging schemes:
  - Diffusion weightings (b-values)
  - Diffusion directions

  on estimated DKI parameters

- To find an optimal DKI imaging schemes within a clinically feasible image acquisition time (< 10min)

Diffusion Weighted Imaging Schemes

4 DKI dataset, each with: b_1 b_2 b_3 b_4 b_5

5 b-values: b = 500, 1000, 1500, 2000, 2500 s/mm²

64 diffusion directions

Acquisition time: 30 min×4

Full Dataset

Diffusion Weightings (b-value)

Diffusion Directions

$Nbval_2$ $Nbval_3$ $Nbval_4$ $Nbval_5$ $Ndir_{15}$ $Ndir_{30}$ $Ndir_{45}$ $Ndir_{64}$

$Nbval_2$:
b_2, b_4
b_2, b_5
Optimal

$Nbval_3$:
b_1, b_2, b_4
b_1, b_2, b_5
b_2, b_3, b_4
b_2, b_3, b_5
b_2, b_4, b_5
Optimal

$Nbval_4$:
b_1, b_2, b_3, b_4
b_1, b_2, b_3, b_5
b_2, b_3, b_4, b_5
b_1, b_2, b_4, b_5
Optimal

Optimal imaging schemes

Diffusion weighted imaging schemes were constructed by taking subsets from the full DKI datasets.

Experiment 1: Find the optimal b-value subset

Experiment 2: Find the optimal combinations of numbers of b-values and diffusion directions

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Methods

- Both regions of interests (ROI) and whole brain analysis
- For ROI analysis, four regions are selected:

Genu   Internal capsule   Thalamus   Basal ganglia
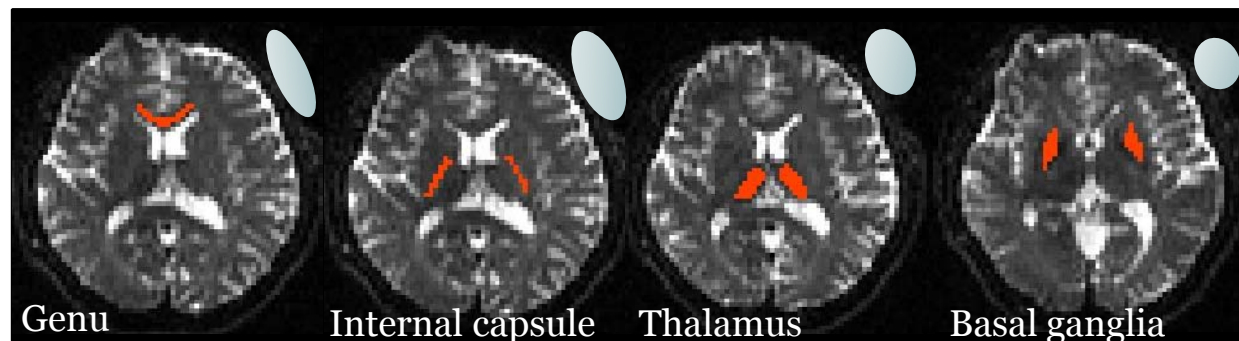
- In order to minimize directional bias for the chosen Ndir sets to the tensor direction in each ROI, eight maximally different subsets of 15, 30 and 45 diffusion directions were chosen from the full 64 direction set

  - Based on minimizing electrostatic energy of the direction vectors

  - 32 data points for each ROI (4 repeats x 8 subsets)

Effect of Diffusion Weighting Selections

Estimation Accuracy — Estimation Variability
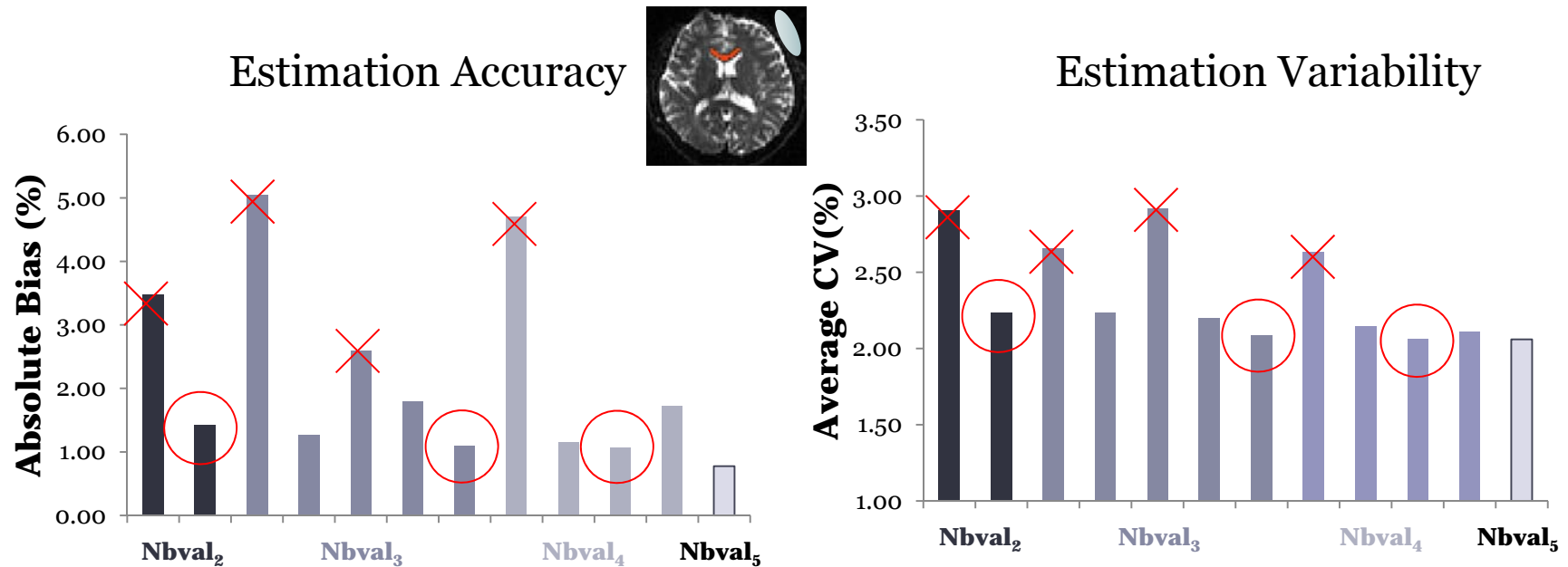
- All sets with b_{max} of 2000 s/mm² have higher bias and variability

- Optimal b-value subsets:

    Nbval$_2$: b = 1000, 2500 s/mm²
    Nbval$_3$: b = 1000, 2000, 2500 s/mm²
    Nbval$_4$: b = 1000, 1500, 2000, 2500 s/mm²

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Effect of Numbers of b-values and Diffusion Directions
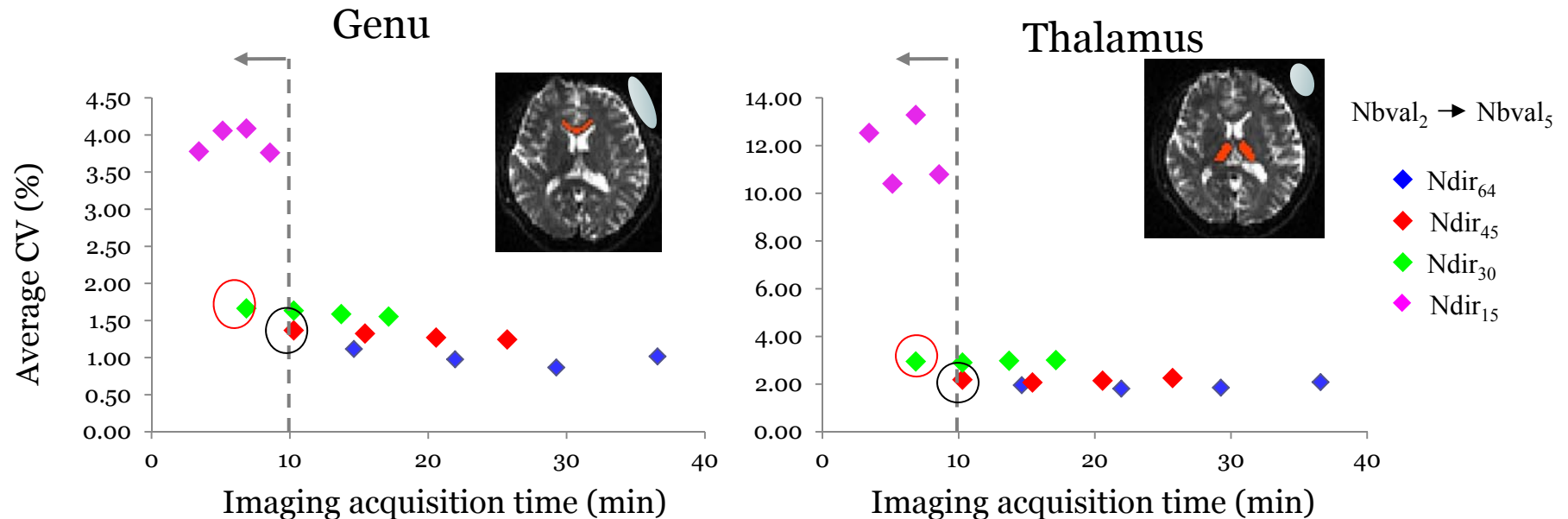
Opt7min: Nbval = 2 (b = 1000, 2500 s/mm²), Ndir = 30

Opt10min: Nbval = 2 (b = 1000, 2500 s/mm²), Ndir = 45

- How do they perform compared to already proposed DKI imaging schemes?

Orig17min[1]: Nbval = 5 (b = 500, 1000, 1500, 2000, 2500 s/mm²), Ndir = 30 (~17

Orig7min[2]: Nbval = 2 (b = 1000, 2000 s/mm²), Ndir = 30 (~7min)

Gold Standard: Full data (Nbval = 5, Ndir = 64, average of 4 repeats)

[1] Jensen JH, et al. 2005; [2]Jensen JH & Helpern JA. 2010.   7

Performance of Different Imaging Schemes

K_r

Gold standard   Orig17min   Orig7min   Opt7min   Opt10min

Difference Map
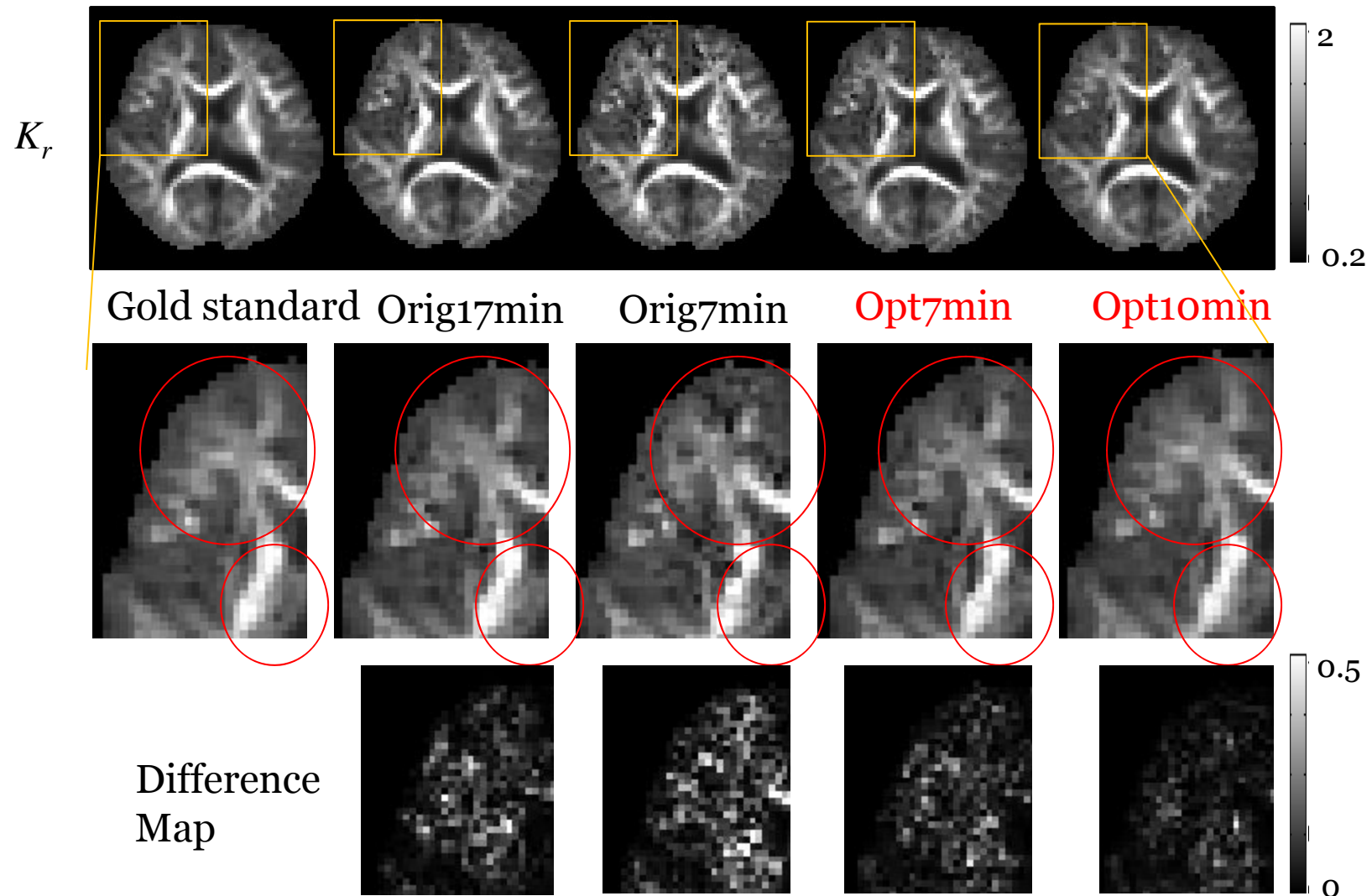
- Opt10min > Opt7min ≈ Orig17min > Orig7min

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Estimation Variability in Whole Brain

White matter (WM)

Grey matter (GM)

Cerebrospinal fluid (CSF)

WM   GM
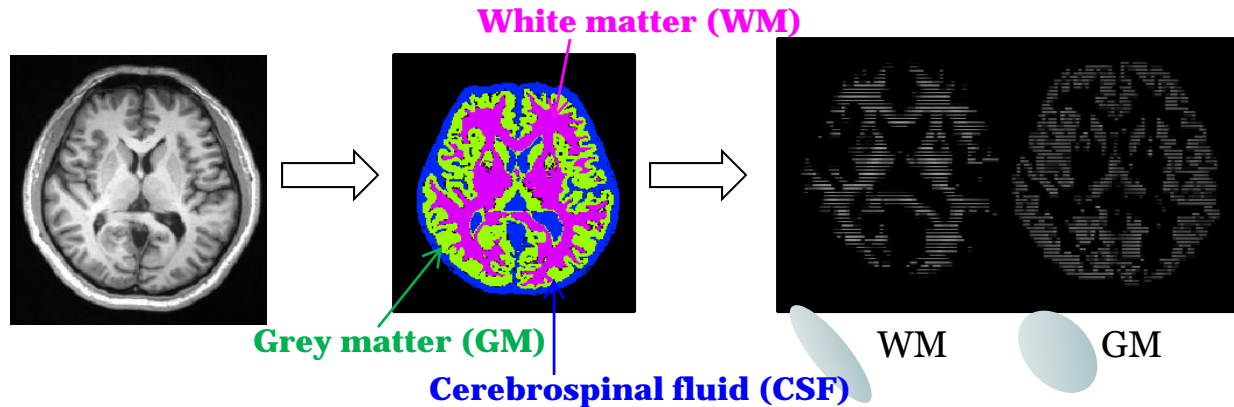
1: Orig17min

2: Orig7min

3: Opt7min

4: Opt10min

Variability across four repeated measurements

☐ GM

☐ WM

MK K_a K_r
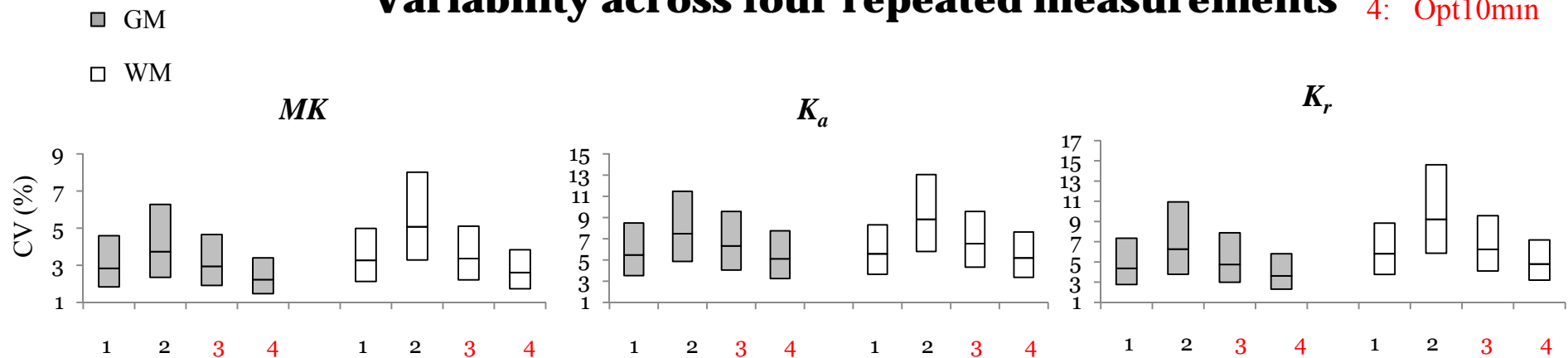
Box shown are median, 25th and 75th value

•Variability: Opt10min < Orig17min < Opt7min < Orig7min

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Estimation Accuracy in Whole Brain

□ GM

□ WM

Average bias from four repeated measurements

1: Orig17min

2: Opt7min

3: Opt10min

MK

K_a

K_r

Box shown are median, 25th and 75th value
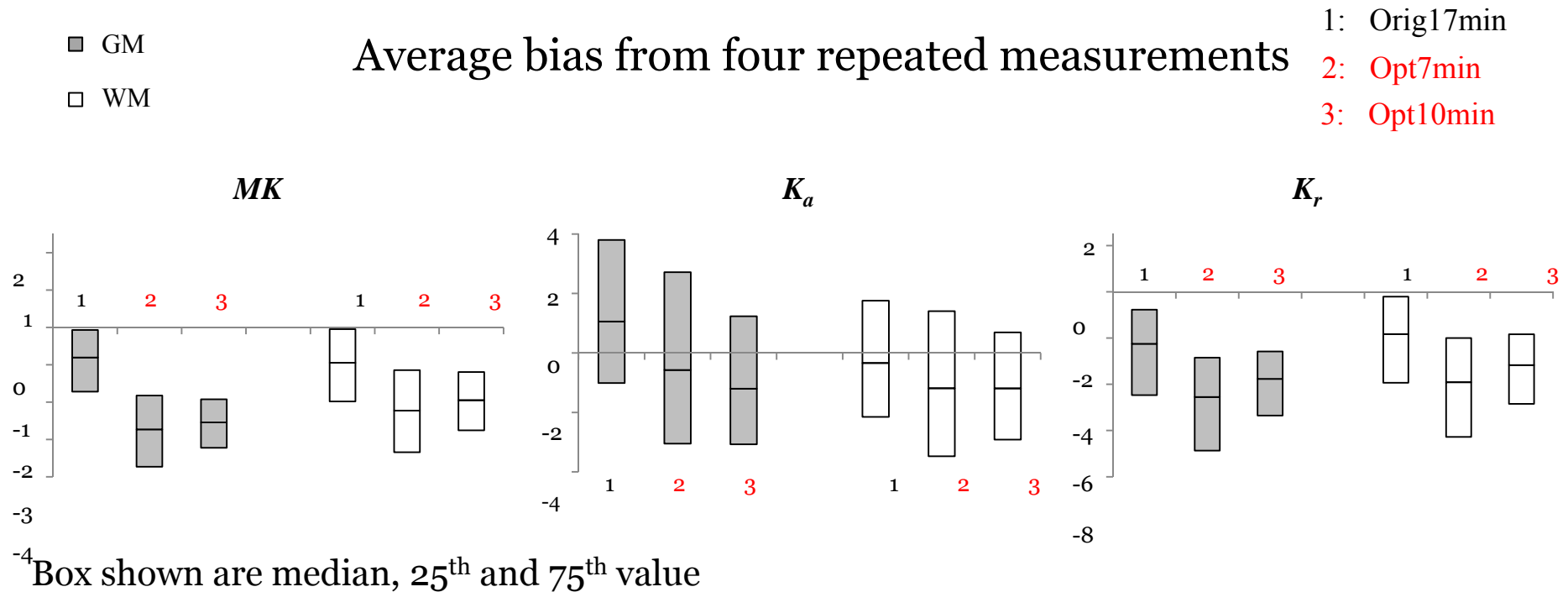
- The Orig7min scheme has much higher bias due to a different b_{max} (not shown)
- Accuracy: Orig17min > Opt10min > Opt7min
- Bias for Opt10min may be systematic (lower spatial variability)
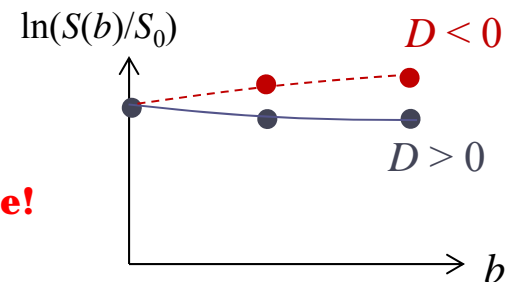- Negative bias in MK and K_r is noise related

How Does Image Noise Affect DKI Fitting

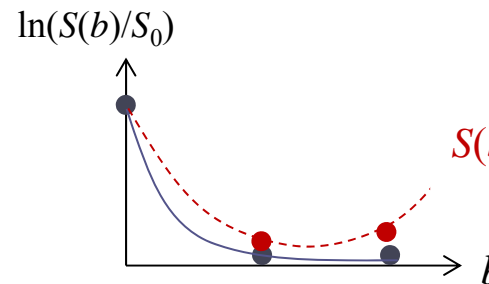- Diffusion parameters have to be physically meaningful.

Principle of diffusion MRI:

$\ln(S(b)/S_0)$ $\quad D < 0$

➤ $S_0 > S(b)$ ⟹ Constraint 1: $D \geq 0$

$D > 0$

Constraint violations for DTI parameters are Rare!

b

➤ $S(b_1) > S(b_2)$, if $b_1 < b_2$

$\ln(S(b)/S_0)$

⟹ Constraint 2:
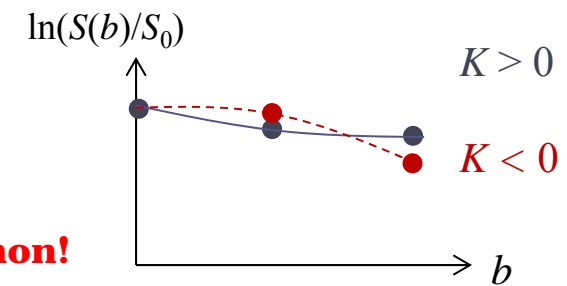$K \leq K_{max} = 3/(D \cdot b_{max})$

$S(b)$ not monotonically decreasing

$$\ln\frac{S(b)}{S_0} = -bD + \frac{1}{6}b^2 D^2 K$$

b

From multi-compartment model and empirical evidence[*]:

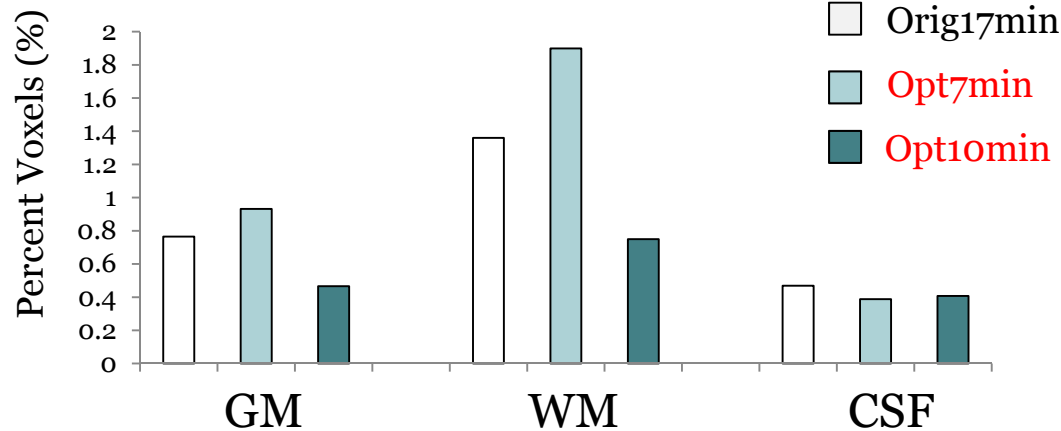➤ $\ln(S(b)/S_0)$ is a convex function of b ($K > 0$)

$\ln(S(b)/S_0)$

$K > 0$

⟹ Constraint 3: $K \geq 0$

$K < 0$

Constraint violations for DKI parameters are very common!

b

[*]Tabesh et al., Magn Reson Med. 2011

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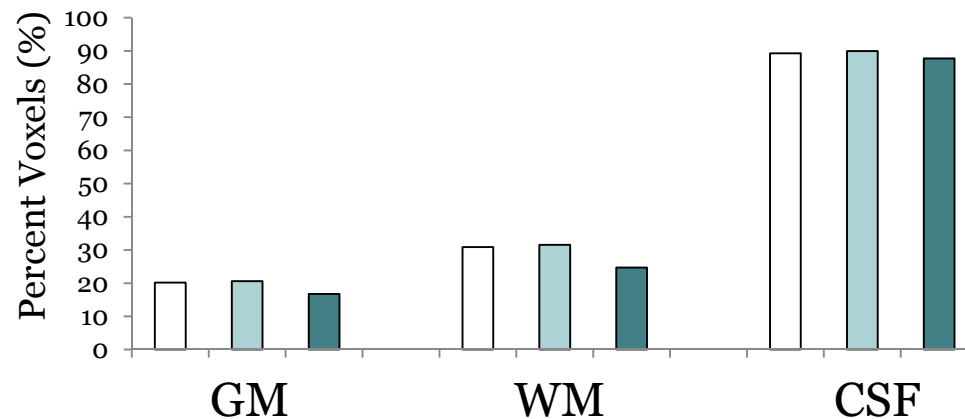
Constraint Violations of Different Imaging Schemes

Voxels with $K < 0$

Method: Count voxels which violated different constraints*
- Negative diffusivity ($D < 0$)
- Negative kurtosis   ($K < 0$)
- Kurtosis value over limit
  ($K \leq K_{max} = 3/(D \cdot b_{max})$)

Voxels with $K > K_{max}$

• Voxels with $D < 0$ is rare ($< 0.5\%$) (now shown here)

• Percent voxels violations:
  Opt10min < Orig17min < Opt7min

*Tabesh et al., Magn Reson Med. 2011

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Conclusion

- Overall DKI estimation benefit more from increased number of diffusion directions than number of diffusion weightings.
  - More diffusion directions reduces estimation variability of DKI parameters.
  - More diffusion weightings increases estimation accuracy.

- The optimal DKI imaging schemes are with two diffusion weightings. With 45 diffusion directions, the optimal imaging scheme even improves upon the conventional imaging with 17 min.

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